STATISTICAL ANALYSIS PLAN (SAP)

Treatment: Once Nightly Formulation of Sodium Oxybate for Extended Release Oral Suspension (FT218) for Excessive Daytime Sleepiness and Cataplexy

Study Title: A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

Randomized study **E**valuating the efficacy and **S**afe**T**y of a **ON**ce nightly formulation of sodium oxybate (REST-ON Study)

SAP Version:	Version 4: Final: 31 July 2019
Protocol Number:	CLFT218-1501
EudraCT Number:	2016-000359-29
IND Number:	126321
Investigational Product:	Sodium Oxybate for Extended-Release Oral Suspension (FT218)
Phase:	3
Sponsor:	Flamel Ireland Limited Blanchardstown Corporate Park Block 10-1, Ballycoolin Dublin 15 Ireland

Flamel Ireland Limited, a wholly owned subsidiary of Flamel Technologies

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APPROVAL SIGNATURES FOR SAP

Study Title: A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

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Date: 31 July 2019

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

%	Percentage
ADR	Adverse Drug Reaction
AE	Adverse Event
CGI	Clinical Global Impression
CR	Controlled Release
[redacted]	[redacted]
eCRF	Electronic Case Report Form
EDS	Excessive Daytime Sleepiness
[redacted]	[redacted]
FAS	Full Analysis Set
FWER	Family-Wide Error Rate
FT218	Sodium oxybate for extended-release oral suspension
[redacted]	[redacted]
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
ITT	Intent To Treat
MMRM	Mixed-effects Model for Repeated Measures
MWT	Maintenance of Wakefulness Test
NCA	Number of Cataplexy Attacks
NT1	Narcolepsy Type 1
NT2	Narcolepsy Type 2
PGI	Patient Global Impression
PPS	Per Protocol Set
PSG	Polysomnogram

PT Preferred Term

SAE Serious Adverse Event

SAP Statistical Analysis Plan

SSDD Sleep and Symptom Daily Diary

SOC System Organ Class

[redacted]

SS Safety Set

TEAE Treatment Emergent Adverse Event

TESAE Treatment Emergent Serious Adverse Event

TFL Tables, Listings and Figures

VAS Visual Analog Scale

1 INTRODUCTION

Sodium Oxybate is indicated for the treatment of excessive daytime sleepiness (EDS) and cataplexy in adults with narcolepsy. Flamel proposes a new sodium oxybate drug product based on its Micropump® technology, Sodium oxybate for extended-release oral suspension (FT218), to be taken once at bedtime. Sodium Oxybate has shown significant efficacy for treating EDS and cataplexy in narcolepsy.

1.1 STUDY RATIONALE

This study was designed as a pivotal efficacy study. The background data used to design the trial was obtained from a Phase I (PKFT218-1301) pharmacokinetic study in healthy volunteers. In that study the 4.5 g FT218 formulation was associated with a safety profile and total exposure similar to the reference marketed drug product, Xyrem®. Also, no safety concerns emerged with the FT218 formulation at 6 g and 7.5 g. The study confirmed the expected PK properties of the FT218 formulation, i.e. a drug release over 6 hours, a lower C_{max} and a residual plasma level at 8 hours after intake that was not significantly different from Xyrem®. These results indicate that the FT218 formulation should be as safe as Xyrem®. Overall, the PK profile of FT218 at 4.5 g, 6 g, and at 7.5 g supports the hypothesis that the IMP is as safe as the reference, Xyrem®.

The forced up-titration design is intended to inform an appraisal of the benefits and risks of increasing doses. Three target therapeutic dose levels will be tested since a concentration/response relationship has not been established. The 6 g, 7.5 g and 9 g doses were selected for their safety and efficacy profile in treating patients with EDS and cataplexy; the study formulation has been found to be safe at 4.5 g, 6 g and 7.5 g in healthy volunteers. The up-titration schedule from 4.5 g/night to 6 g/night is based on the dosage schedule recognized as safe with the reference product. Further 1.5 g increments commence after a period sufficiently long to permit evaluation of efficacy. Subjects remain on the 6 g dose for two weeks, on the 7.5 g dose for five weeks and on the 9 g dose for five weeks.

1.2 CHANGES FROM PROTOCOL

N.A. This is a Special Protocol Review.

1.3 DEFINITION OF ANALYSIS POPULATION

The target population is individuals in need of treatment of EDS and cataplexy in patients with narcolepsy. The full analysis population for efficacy is the intent to treat population including all randomized subjects with at least one efficacy measurement at the time of the 6 g dose (whether FT218 or placebo.)

2 STUDY SUMMARY

This is a double-blind, randomized, placebo controlled, two arm multi-center forced up-titration study to assess the efficacy and safety of a once nightly formulation of Sodium Oxybate (FT218) for the treatment of EDS and cataplexy in patients with narcolepsy. The active arm will have forced dose increments at fixed times from 4.5 g/night followed by 1.5 g/night increments until the final 9 g dose is reached. Subjects will remain on the 4.5 g dose for one week, the 6 g for two weeks, the 7.5 g for five weeks and the 9 g dose for five weeks. The primary contrasts are between the 9 g dose and the corresponding placebo outcomes. If the 9 g dose is statistically significant, the 7.5 g dose and the corresponding placebo outcomes will be compared. If the 7.5 g dose is statistically significant, the 6 g dose and the corresponding placebo outcomes will be compared.

There are two types of narcolepsy patients to be studied. Patients with Narcolepsy Type 1 (NT1) who present with excessive daytime sleepiness (EDS) and cataplexy and patients with Narcolepsy Type 2 (NT2) who present with EDS (without cataplexy). For both NT1 and NT2, the historical Multiple Sleep Latency Test (MSLT) must indicate 2 or more sleep-onset REM periods (SOREMPs), the mean sleep latency on MSLT must be in the pathological range (i.e. <8 minutes) and no other sleep disorder better explains the EDS.

The endpoints for evaluating EDS in both NT1 and NT2 narcolepsy patients are the mean sleep latency on the Maintenance of Wakefulness Test (MWT), and the Clinician Global Impression (CGI) for sleepiness. The endpoint for evaluating cataplexy in NT1 narcolepsy patients is the number of cataplexy attacks (NCA) obtained from the Sleep and Symptom Daily Diary.

2.1 OBJECTIVES

To compare the safety and efficacy of 6 g, 7.5 g and 9 g doses of FT218 to placebo in the treatment of symptoms in patients with Narcolepsy.

2.1.1 PRIMARY OBJECTIVES

- To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating EDS in both NT1 and NT2 subjects as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT) and by the Clinical Global Impression (CGI) rating of sleepiness

- To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating cataplexy in NT1 subjects as measured by the number of cataplexy attacks (NCA) determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary

2.1.2 SECONDARY/EXPLORATORY OBJECTIVES

The secondary/exploratory objectives of the study are to compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo for [redacted]

[redacted]

2.1.3 Safety Objective

To evaluate the relative safety of the 6 g, 7.5g and 9 g doses of FT218 compared to placebo.

2.2 Study Design

This is a double-blind, randomized, placebo controlled, two arm multi-center forced up-titration clinical trial to assess the efficacy and safety of a once per night formulation of Sodium Oxybate (FT218) for the treatment of EDS and cataplexy in patients with narcolepsy. The active arm will have forced dose increments at fixed times from 4.5 g/night followed by 1.5 g/night increments until the final 9 g dose is reached. Subjects in the active arm will remain on the 4.5 g dose for one week, 6 g for two weeks, 7.5 g for five weeks and the 9 g dose for 5 weeks.

2.3 Schedule of Events

The clinical trial design is comprised of four periods: screening, wash-out/baseline (which includes randomization), double-blind-treatment and follow-up. These are shown in Table 1. After randomization, the doses of the FT218 arm begins at 4.5 g where it remains for one week (Period 3a), then it is titrated to 6 g where it remains for two weeks (Period 3a), then to 7.5 g where it remains for five weeks (Period 3b (i) and 3b (ii)) and finally to 9 g for the final 5 weeks (Period 3c(i) and 3c(ii)). [redacted]

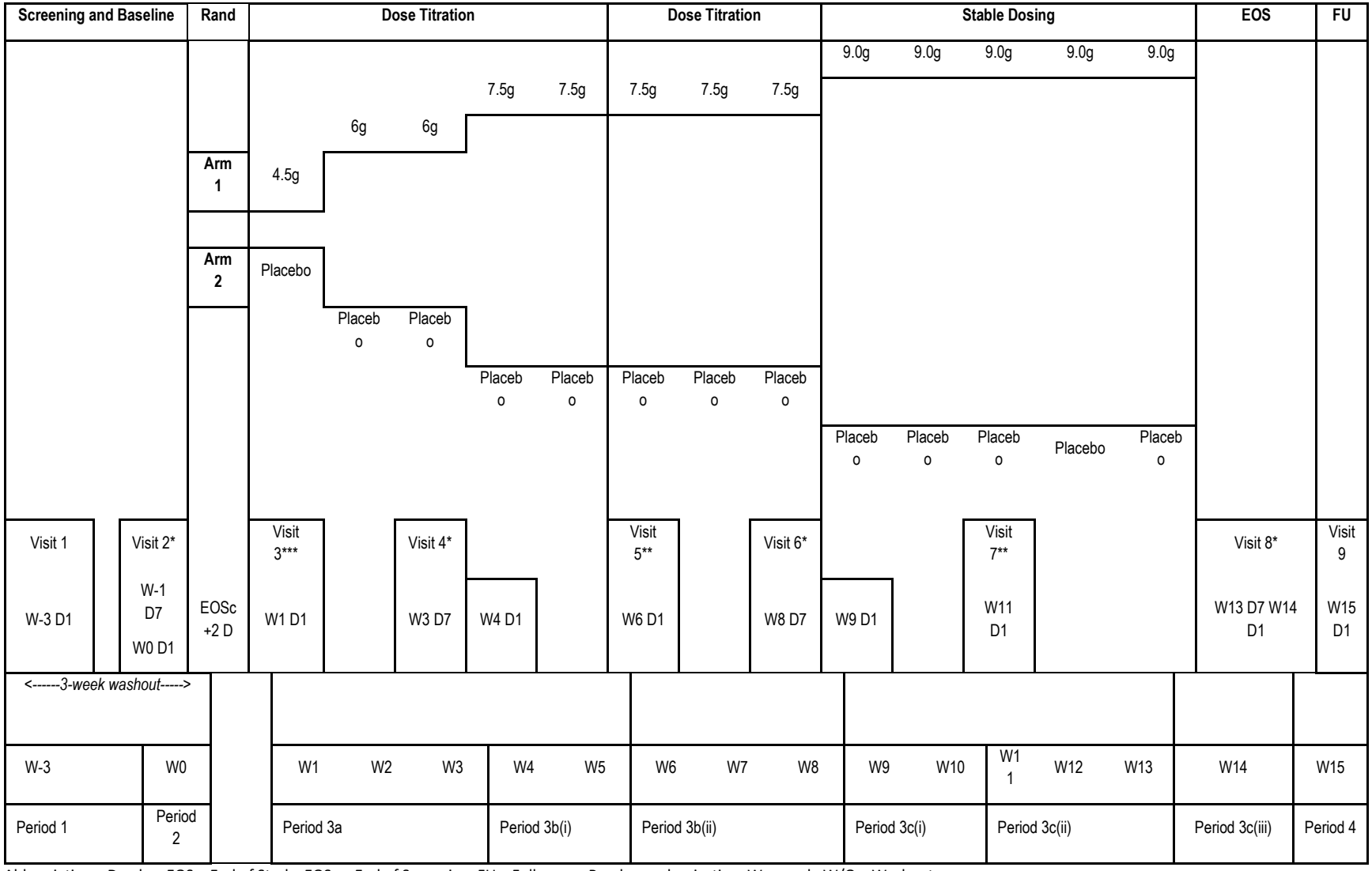
Table 1. Schedule of Events				
Period	**Week(s)**	**Phase of Study**		**Evaluations**
1	**Week -3 to Week 0**	**Week -3** Screening Visit **Week -3 Day 1** Commence Sleep and Symptom Diary **Week -1 D7** Overnight PSG and next day 4 Nap MWT		*Full screening and enrolment evaluation* *Full Baseline Evaluation (D7 W-1 – PSG; D1 W0 Next day MWT)*
2	**Week 0*** **	**Week 0 + Max 2 days** Central Scoring Lab Results **Week 0 D2 or D3** Randomization		
		FT218 Arm	**Placebo Arm**	
3a	**Weeks 1-3**	Week 1: 4.5g Week 2-3: 6.g	Placebo	*Full Efficacy Assessment* Visit 4 (D7 Week 3 and D1 Week 4)*
3b(i)	**Weeks 4-5**	*7.5 g*	*Placebo*	
3b(ii)	**Weeks 6-8**	*7.5 g*	*Placebo*	*Partial Efficacy Assessment** done at Visit 5 (D1 Week 6)* *Full Efficacy Assessment* at Visit 6 (D7 Week 8 and D1 Week 9)*
3c(i)	**Weeks 9-10**	*9g*	*Placebo*	
3c(ii)	**Weeks 11-13**	*9 g*	*Placebo*	*Partial Efficacy Assessment** at Visit 7 (D1 Week 11)* *Full Efficacy Assessment* at Visit 8 (D7 Week 13 and D1 Week 14)*
3c(iii)	**Week 14**	*End of Study Visit (EOS)*		
4	**Week 15**	*Follow-up Visit*		

1.* Full efficacy assessment occur on the last day of a period and extend into the following day of the next period.

2.** Partial efficacy assessment (MWT and PSG are excluded) occur following the first two weeks on the 7.5 g dose and following the first two weeks on the 9 g dose during respective periods.

3.*** Maximum of 2 day turnaround for PSG and MWT results from Central Scoring Laboratory

Table 2: Study Design



Abbreviations: D = day, EOS = End of Study, EOSc = End of Screening, FU = Follow-up, Rand = randomization, W = week, W/O = Washout

2.4 Sample Size Determination

Estimation of sample size to achieve a desired power depends on the number and nature of the hypothesis testing paradigm and assumptions about the magnitude of the underlying effects. In this trial, hypothesis testing will proceed in the following order. First MWT and CGI will be examined for statistical significance in the full sample including both NT1 and NT2 patients for the 9 g dose. If significant, NCA for the same dose will be tested in NT1 patients. If the first test fails, the data for this dose is not able to reject the null hypothesis of equality to placebo. If the first test is significant, but the second fails, the dose has been demonstrated to be superior to placebo for EDS treatment, but not for cataplexy. If both tests are statistically significant, the dose has been shown to be effective for both EDS and cataplexy treatment. The same sequence of testing will be followed for the 7.5 g dose. If both tests are statistically significant, the dose has been shown to be effective for both EDS and cataplexy treatment and the same sequence of testing will then be followed for the 6 g dose. Each dose will be tested at the two-sided alpha level of 0.05.

2.5 RANDOMIZATION AND BLINDING

[redacted]

2.5.1 INTERIM ANALYSIS AND UNBLINDING.

There are no planned interim analyses. Other than individuals unblinded for safety issues, the data will remain blinded until after the database is locked.

2.5.2 DATA AND SAFETY MONITORING BOARD (DSMB)

An independent DSMB will be appointed to review and assess study conduct and safety for the duration of the clinical trial.

2.6 STUDY ENDPOINTS

The endpoints for evaluating EDS in both NT1 and NT2 narcolepsy patients are the Maintenance of Wakefulness Test (MWT), Clinician Global Impression (CGI) and secondarily the Epworth Sleepiness Scale (ESS).

The endpoint for evaluating cataplexy in NT1 narcolepsy patients is the mean number of daily cataplexy attacks (NCA) as determined from the Sleep and Symptom Daily Diary during the Period

[redacted]

2.6.1 PRIMARY ENDPOINTS FOR EFFICACY

2.6.1.1 PRIMARY ENDPOINTS FOR EDS

The co-primary endpoints for evaluating EDS in both NT1 and NT2 narcolepsy patients is mean sleep latency on the Maintenance of Wakefulness Test and the Clinician Global Impression for sleepiness. The MWT is the mean latency across 5 naps, averaged over the test day and the CGI is the clinician's global impression of improvement in daytime sleepiness.

2.6.1.2 PRIMARY ENDPOINT FOR CATAPLEXY

The primary endpoint for evaluating cataplexy is the number of cataplexy attacks, which will be evaluated only on the narcolepsy NT1 subpopulation. The NCA is the mean number of cataplexy events recorded on the Sleep and Symptom Daily Diary (SSDD) during the Period. Because of concern about the variability of this measure, a minimum number of diary entries of 3 per week is required for the average to be considered an observation. If

the number of days with entries is less than three, the mean NCA for that week will be considered missing.

2.6.2 SECONDARY/EXPLORATORY ENDPOINTS

The secondary/exploratory efficacy endpoints are

[redacted]

2.6.3 ENDPOINTS FOR SAFETY

Safety will be evaluated based on reports of adverse events either spontaneously reported or observed in clinical laboratory analyses. All adverse events and all serious adverse events will be tabulated by system organ class and preferred term.

3. ANALYSIS SETS

The intent to treat and per protocol populations form the bases for the evaluation of efficacy. The safety population forms the basis for the evaluation of safety.

3.1 THE INTENT TO TREAT (ITT) POPULATION

The ITT population includes all randomized subjects with at least one efficacy measurement after receiving the 6 g dose (whether FT218 or placebo.) A valid diary measurement is defined to include at least 3 days of entries per week. Diary measurements with fewer days will be treated as missing, and if there are no other measurements will not

qualify the subject for the ITT population. Patients will be assigned to treatment groups in the analysis as randomized.

3.2 THE PER PROTOCOL (PP) POPULATION

The PP population includes all subjects in the ITT population reduced by those who failed to follow the protocol with respect to protocol deviations. These are inclusion or exclusion criteria not satisfied (protocol chapter 8, sub-sections 8.3.2 and 8.3.3), deviations related to study drug administration, deviations to the schedule of visits and procedures (protocol chapter 9) or deviations related to concomitant medications not permitted (protocol chapter 8, sub-section 8.4.8.1). Subjects will be assigned to treatment groups as randomized.

3.3 THE SAFETY (S) POPULATION

The S population includes all subjects that receive at least one dose of study medication. Subjects will be assigned to treatment group based on the treatment actually administered.

4. DESCRIPTION OF STATISTICAL ANALYSIS

The formal statistical analysis and specific dose/placebo contrasts will be based on a mixed-effects repeated measures (MMRM) means model or a corresponding generalized mixed-effects model (GLIMMIX) in case of categorical data. Descriptive statistics characterizing the study population and the observed outcomes will be produced.

4.1 GENERAL CONSIDERATIONS

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise specified. The null hypothesis for all tests is that FT218 and placebo have equal means. All sample mean outcome differences between the study treatments/doses will be reported with 95% confidence intervals. The *p*-value will be presented for each statistical test; if the value is less than 0.05, 0.01 or 0.001, the result will be highlighted by the respective annotation *, ** or ***.

Descriptive statistics will be provided by dose group and as a summary across all dose groups.

4.1.1 STANDARD DESCRIPTIVE STATISTICS

CONTINUOUS VARIABLES

Standard descriptive statistics will be reported for continuous variables including number of non-missing observations, mean, median, standard deviation, 95% confidence interval for the mean, median, inter-quartile range, minimum, and maximum value.

CATEGORICAL VARIABLES

Standard descriptive statistics will be provided for categorical variables in contingency tables with cell frequencies and percentages for the number of non-missing observations. Entries will include total number, number missing, number available, number for each category, and the corresponding percentage of the total number of values available for each category.

4.1.2 DEFINITION OF STUDY VISITS

Study visits are identified by the week of the visit.

At Week -1 (Baseline) a full baseline evaluation will take place. Thereafter with full efficacy assessments occurring at week 3 for the 6 g dose, week 8 for the 7.5 g dose and week 13 for the 9 g dose. Visits with partial efficacy assessments (MWT and PSG are excluded) occur following the first two weeks on the 7.5 g dose (week 6 day 1) and following the first two weeks on the 9 g (week 11 day 1).

4.1.3 ANALYSIS ASSESSMENT WINDOWS

Comparison between specific doses and placebo utilize measurements from comparable periods in the study. Thus, there will be 3 sets of placebo measurements; one corresponding to the 6 g dose (weeks 2 and 3), one corresponding to the 7.5 g dose (weeks 4 through 8) and one corresponding to the 9 g dose (weeks 9 through 13.)

4.1.4 TREATMENT START/STOP DATES

Treatment in the FT218 arm will begin on Day 1, Week 1 at 4.5 g dose. The dose will be increased to 6 g on Day 1, Week 2 and to 7.5 g on Day 1, Week 4. The dose will increase to 9 g on Day 1, Week 9 and continue at that dosage until Day 7, Week 13.

4.1.5 TABLES, LISTINGS AND FIGURE PRESENTATION

The treatment groups will be displayed in the tables, listings and figures as

Group 1:	9 g	(Period 3c (i) and 3c (ii), weeks 9-13)
Group 2:	Placebo	(Period 3c (i) and 3c (ii), weeks 9-13)
Group 3:	7.5 g	(Period 3b (i) and 3b (ii), weeks 4-8)
Group 4:	Placebo	(Period 3b (i) and 3b (ii), weeks 4-8)
Group 5:	6 g	(Period 3a, weeks 2-3)
Group 6:	Placebo	(Period 3a, weeks 2-3)

The listings will display all of the data contained in the eCRF. The listings will be ordered by the treatment groups shown above.

Summaries of continuous variables will use the following descriptive statistics: n, mean, standard deviation, 95% confidence interval of the mean, median, interquartile range, minimum and maximum.

The number of decimal places to be displayed for each statistic will be as follows:

- Mean, 95% confidence intervals, median and interquartile range: one more decimal place than data.
- Standard deviation: two more decimal places than the data.
- Minimum and maximum: same number of decimal places as the data.
- P-value: 3 decimal places, if less than 0.001 then display as "<0.001".

Categorical variables will be presented as frequency counts and percentages. Percentages will be displayed to one decimal place throughout.

All dates will be displayed in the format DDMMMYYYY

Calculations using dates will follow these conventions:

The relative study day of the event (DAY) is calculated as the difference between the date of the event of interest (EVENT DAY) and the date of first dose of study medication (FIRST DOSE), i.e.

DAY = EVENT DATE - FIRST DOSE + 1 for EVENT DATE ≥ FIRST DOSE

DAY = EVENT DATE - FIRST DOSE for EVENT DATE < FIRST DOSE

Durations will be calculated by: DURATION = (STOP DATE - START DATE) + 1

4.1.6 USE OF ANALYSIS SETS

For the primary statistical analyses of efficacy endpoints, the ITT will be used; a supportive analysis will be carried out on the PP population unless it is essentially the same as the ITT population, if the difference in sample sizes is less than 10%. All safety endpoints analysis will be conducted on the Safety population.

4.1.7 ANALYSIS OF SUBGROUPS

The primary efficacy analyses for EDS will be performed on the full ITT population. The primary efficacy analyses for cataplexy will be performed on the NT1 subgroup of the ITT population.

[redacted]

4.2 SUBJECT DISPOSITION

The number of subjects within each dose of each analysis population will be summarized. The number of subjects entering each Period of the study will be tabulated along with number of subjects who withdraw. The timing of withdrawal and reasons for withdrawal (adverse event, lost to follow-up, withdrawal by subject, withdrawn due to physician decision, non-compliance with study drug, due to pregnancy, lack of efficacy, death, other reasons) will be summarized by treatment for each Period of the study and summarized over all Periods in the randomization stage.

4.3 DEMOGRAPHICS AND BASELINE SUBJECT CHARACTERISTICS

Subject demographics will be presented by treatment arm and for the total study. Baseline will be defined as the measurement in Period 2, prior to randomization. Initial data at screening will also be reported for all screened subjects.

Cases for which the entry criteria or other protocol requirements were violated will be identified and their baseline characteristics will be summarized.

4.4 MEDICAL HISTORY

Medical history data will consist of significant conditions or diseases recorded during the screening process. Data will be tabulated using the MedDRA primary system organ class (SOC) and preferred term for subjects in the safety population.

4.5 STUDY DRUG EXPOSURE AND COMPLIANCE

Study drug exposure and duration in the study will be derived based on first and last dose taken. Compliance will be computed as percentage of medication taken.

4.6 EFFICACY ANALYSIS

Two patient populations, one with both narcolepsy symptoms (EDS and cataplexy) and one with only EDS will be studied in a single parallel groups, dose-escalation design. The treatments are placebo and increasing doses of the test drug, FT218. Two primary outcome measures, MWT and CGI quantify the treatment effect on EDS and the NCA is the primary

outcome measure for cataplexy. All ITT or PP subjects will be included in the evaluation of EDS and all ITT or PP subjects with both conditions will be used in the evaluation of cataplexy.

Subject demographics and baseline characteristics will be tabulated for all randomized subjects. The baseline comparability of treatment groups with respect to subject demographics and baseline characteristics will be described, but formal statistical tests will not be performed.

4.6.1: PRIMARY ANALYSIS:

A mixed effect repeated measures (MMRM) means model will be used to analyze change from baseline for MWT and cataplexy. Each model will include treatment, time (at which the measurement was taken), treatment-by-time interaction, site and baseline score as fixed effects and subjects as random effects. In fitting the model, time will range over the entire period of observations. [redacted]

For CGI, a GLIMMIX model for binomial data with logit link will be used instead of a MMRM to analyze the categorized CGI response, i.e., proportion of patients who were very much or much improved. The observed values for the categorized response (very much or much improved versus other category) will be used as responses in the model. Each model will include treatment, time (at which the measurement was taken), treatment-by-time interaction and site as fixed effects and subjects as random effects. In fitting the model, time will range over the entire period of observations. The odds ratio, 95% confidence intervals for the odds ratio and p-value will be provided.

4.6.2 SEQUENTIAL TESTING APPROACH FOR COMPARING SOCR AND PLACEBO

The primary hypothesis tests of the efficacy of individual doses will be performed as contrasts within the mixed models. The hypothesis testing will proceed in the following order, which is represented pictorially in Figure 1. First to test hypotheses for EDS, both MWT and CGI will be examined, in parallel for statistically significant differences from placebo for the 9 g dose. The order of hypothesis testing and the tests to be performed are displayed in Figure 1. For the 9 g dose, if both tests are significant, NCA for the same dose will be tested. If the first test fails (either MWT or CGI not significant), the data for the 9 g dose was not able to reject the null hypothesis of equality to placebo for either symptom. If the first test is significant (both MWT and CGI significant,) but the second test (NCA) fails, the 9 g dose has been demonstrated to exceed placebo for EDS treatment but not for cataplexy. If both tests are statistically significant, the 9 g dose has been shown to be effective for EDS and for cataplexy. Although all data are included in the full model, the tests for the 9 g dose are contrasts over the Periods 3c(i) and 3c(ii).

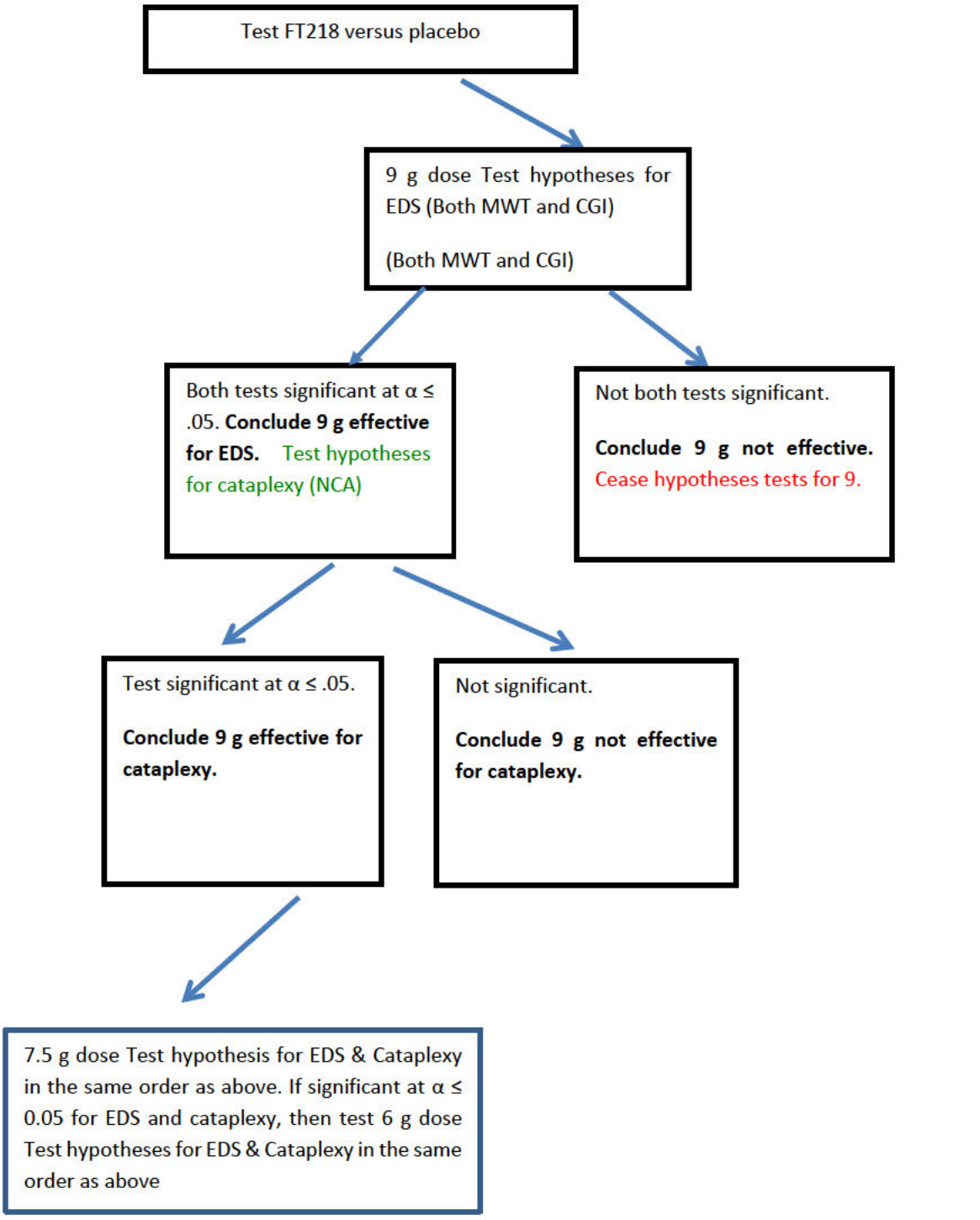
If the 9 g dose demonstrates efficacy for both EDS and cataplexy, the same sequence of testing will be followed for the 7.5 g dose using contrasts over the Periods 3b(i) and 3b(ii). If the 7.5 g dose demonstrates efficacy for both EDS and cataplexy, the same sequence of testing will be followed for the 6 g dose using contrasts over Period 3a.

Each dose will be tested at the two-sided alpha level of .05. Efficacy tests for MWT and for CGI within a dose need not be adjusted, since both are required for demonstrating efficacy for EDS at that dose. Efficacy tests for NCA within a dose for demonstrating efficacy for cataplexy also need not be adjusted because the test is reached via a step down procedure. Within each arm, rejection terminates all subsequent hypothesis tests, which will be deemed to be non-significant. A strictly exploratory analysis examining secondary/exploratory endpoints is also proposed to provide evidence of consistency. The Type I error rate for these endpoints will all be tested at the alpha level of .05.

N.B. The testing of the efficacy of the 6 g dose is intended to address the question of identifying the minimally effective dose. If the 9 g dose and then the 7.5 g dose is effective on the primary outcome variables, hypothesis tests on the efficacy of the 6 g dose will be carried out.

[redacted]

Figure 1



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4.7 SAFETY ANALYSES

Safety evaluations will be performed on the safety population using the actual treatment administered.

Adverse events will be identified as treatment-emergent (TEAE) if the event occurs or increases in severity after the first dose of study medication is taken. Adverse events will be identified as mild, moderate or severe and related to the treatment as reported on the CRF. The adverse events will be assigned a preferred term (PT) and a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), latest version .In counting the number of events reported, a continuous event, i.e., an event reported more than once and which did not cease, will be counted only once with the worst recorded severity. Non-continuous AEs reported multiple times by the same subject will be counted as multiple events. AEs will be assigned to the period of the study corresponding to the time of onset. Events presenting immediately prior to the first dose of study medication that do not worsen in severity, will not be included. In deriving the tabulation relating to preferred term reporting, the severity of a recurrent AE will be taken to be the most severe and the relationship to study medication as the most probable within the relevant period of the study. Total exposure to FT218 will be determined in terms of number of days and dose.

Laboratory data will be summarized in terms of the proportions of patients with clinically notable abnormalities using normal ranges. Shift tables will tabulate baseline to most extreme post baseline values. Summary statistics of raw data and change from baseline values will be obtained including means, medians, standard deviations and ranges will be produced.

The summaries will include subjects in the safety population who have had at least one laboratory test performed after the first study drug administration with an available baseline laboratory value. Baseline values will be measured as the last available measure before taking study drug.

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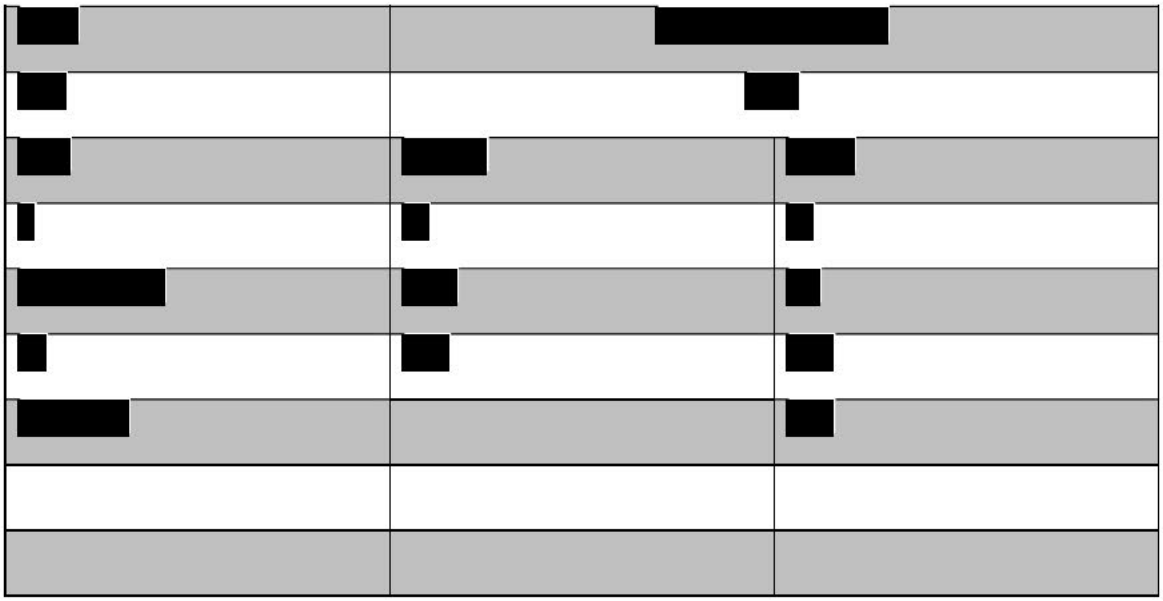

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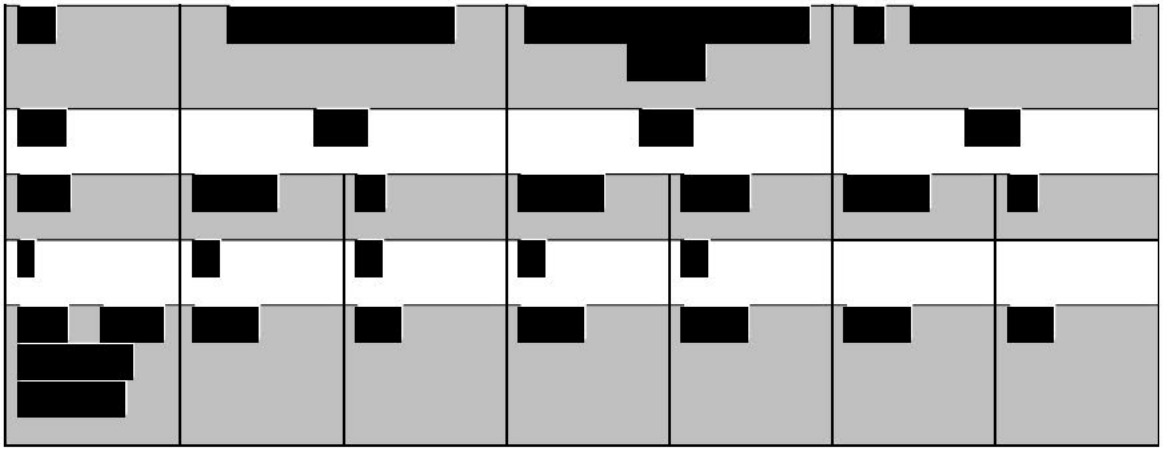

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